## REMARKS

In the most recently received (final) Official Action, the Examiners have rejected pending claims 11-12 respectively under 35 U.S.C. 112, first paragraph as not being enabling for a defined family of short-length PR-39 derived oligopeptides. In addition, The Examiners have rejected pending claims 11-12 respectively under 35 U.S.C. 103(a) as being unpatentable over the Ross *et al.* '233 patent, U.S. Patent No. 6,133,233.

Via this response, applicants have amended presently pending independent claim 11; cancelled dependent claim 12, without prejudice; and added new dependent claims 15 and 16 respectively. Accordingly, by this independent claim amendment, claim cancellation, addition of two new dependent claims, and the discussion presented hereinafter, applicants believe they have overcome and obviated the each basis for rejection stated by the Examiners in the most recent (final) Official Action.

Applicants and their undersigned attorney wish to state their intentions clearly. It is a matter of formal record that this invention and patent application was filed on October 25$^{th}$, 1999; and the prosecution file history to date now is well over five years in duration. Applicants thus sincerely desire to advance the prosecution of this application on the merits, and do not to delay or hinder its progress further. On this premise, therefore, applicants will now address and review each of the different substantive bases for rejection stated by the Examiners in the most recently received

(final) Official Action with regard both to its legal requirements and the relevant factual circumstance

I. The Cancellation of Previously Pending Dependent Claim 12 And The Addition Of New Dependent Claims 15 And 16

It will be noted and appreciated that previously pending dependent claim 12 has now been cancelled (without prejudice). Dependent claim 12 was an exemplary embodiment of the more broadly defined invention of claim 11; defined a 15 amino acid residue short-length analog of PR-39; but was repeatedly seen by the Examiners to be a non-enabled embodiment, despite the quantitative detail and quality of description existing for this exemplary embodiment within the Specification of the instant application.

As a consequence of the present amendments to independent claim 11 and the resulting re-definition and restrictive scope of specific embodiments, dependent claim 12 has been cancelled. Also for these same reasons, new dependent claims 15 and 16 have been added to the instant application. These newly added claims present two different exemplary embodiments, both of which lie within the scope of coverage recited by currently amended independent claim 11.

The Examiners will of course recognize and appreciate that the language of newly added dependent claims 15 and 16 is identical to that of original claims 13 and 14, withdrawn earlier; and that these newly added

claims define two short-length analogs of PR-39, which are respectively 11 and 8 amino acid residues in length. There is, therefore, exact and complete identity of wording between (earlier withdrawn) original claim 13 and new claim 15, as well as between (earlier withdrawn) original claim 14 and new claim 16, except for the difference in claim numbering. Accordingly, the subject matter as a whole comprising applicants' invention is now most broadly defined by currently amended independent claim 11, and is more particularly exemplified by new dependent claims 15 and 16 individually.

II. The Altered Scope Of Applicants' Presently Claimed Invention

Applicants believe that it is useful to summarize briefly what are the altered requirements and restricted scope of their invention as presently claimed in order to identify what applicants' claimed invention actually is, as well as to separate and distinguish the re-defined invention from what it is not.

Applicants' invention is claimed specifically as a "PR-39 derived oligopeptide family". This term, "PR-39 derived oligopeptide family", has been re-defined by currently amended independent claim 11 as a combination of specific elements having particular limitations; and comprises a restricted family whose individual members are pharmacologically active and function to cause a selective inhibition of protease-mediated degradation in-situ after being introduced

intracellularly to a viable cell. It will be noted, however, the membership of the PR-39 derived oligopeptide family has been markedly re-defined and restricted by currently amended independent claim 11.

In addition, two new exemplary embodiments and representative members of this re-defined family of short-length oligopeptides are identified by newly added dependent claims 15 and 16 respectively. New claim 15 recites a precisely recited sequence of 11 amino acid residues; and new claim 16 delineates a precisely recited sequence of 8 amino acid residues. Accordingly, the restricted family membership recited by currently amended claim 11 - which encompasses and includes the exemplary 11 and 8 residue length embodiments presented by newly added claims 15 and 16 - constitutes the full breadth and scope of all the claims now pending in the instant application.

It will be noted also that the wording of presently amended independent claim 11 recites the commonly shared characteristics and properties for the short-length amino acid residue length structures comprising the restricted membership of this PR-39 derived oligopeptide family. Moreover, currently amended claim 11 delineates a carefully circumscribed and size-limited membership which is restricted to PR-39 analog compositions which are less than 14 amino

acid residues in length; and are pharmacologically active, functionally specific, and structurally related as a family of oligopeptides. Equally important, the commonly shared characteristics and properties of the restricted PR-39 derived oligopeptide family members are overtly stated and individually set forth as requisite elements and specific limitations by currently amended independent claim 11; but are set forth as specific amino acid residues in sequence by newly added dependent claims 15 and 16.

Furthermore, it will be appreciated that presently amended independent claim 11 explicitly demands six specific requirements for each member of this family of derived oligopeptides. These requirements are: that the maximum length of each oligopeptide be less than 14 amino acid residues; that each oligopeptide begin with the sequence "Arg-Arg-Arg" at its N-terminal end; that each oligopeptide be devoid of the amino acid sequences "Pro-Pro-X-X-Pro-Pro-X-X-Pro" and " Pro-Pro-X-X-X-Pro-Pro-X-X-Pro" where X is any amino acid; that each oligopeptide be able to be introduced intracellularly to a viable cell; that each oligopeptide be able to interact selectively in-situ with such proteasomes as are present within the cytoplasm of the cell; and that each oligopeptide be able to alter markedly the proteolytic degradation activity of these proteasomes such that a an increased expression of an identifiable peptide occurs in-situ as a consequence.

Within this restricted scope and context, newly added dependent claim 15 provides an 11 amino acid residue length restatement of the broader definition; while dependent claim 16 recites an 8 amino acid residue length restatement. Both of these are representative examples which comply fully and completely with the explicit requirements of currently amended independent claim 11.

III. The Rejection Under 35 U.S.C. 112, 1st Paragraph, Enablement

The Examiners have rejected previously pending claims 11 and 12 under 35 U.S.C. 112, first paragraph, as allegedly failing to provide information sufficient to enable one skilled in the art to make and practice applicants' invention as claimed.

The Examiners have presented their views and position at pages 2-4 in the most recently received (final) Official Action. The essence of their stated rationale is that those skilled in the art are unlikely to accept the data and information disclosed by the Specification text as being correlatable to a 15 amino acid residue and a family of PR-39 derived oligopeptides whose members cause a selective inhibition of proteasome-mediated degradation for at least one identifiable peptide in-situ after introduction intracellularly to a viable cell.

However, the Examiners have also explicitly recognized and repeatedly stated as a matter of formal record that the instant

Specification does provide full enablement for the PR-11 oligopeptide, the 11 amino acid residue length analog. Applicants therefore now trust and rely on the Examiners to stand by their self-expressed view; to uphold their repeatedly stated position that the 11 amino acid residue length analog of PR-39 is fully and completely enabled; and to acknowledge formally that newly added claim 15 (defining the PR-11 oligopeptide) satisfies the enablement requirement of Section 112, 1st paragraph in all respects..

Furthermore, as regards new claim 16 and the 8 amino acid residue length analog of PR-39, applicants submit that the PR-8 oligopeptide is well described and detailed by the instant Specification as to how to make and use this composition of matter. As applicants have shown and documented previously herein, the Specification text not only describes in detail the characteristics and properties of the PR-8 embodiment commonly shared with the PR-39 derived oligopeptide family as a whole at page 25, lines 1-23; but also sets forth the PR-8 oligopeptide residue sequence at page 26, lines 31-32 as one exemplary embodiment of the membership.

In addition, the commonly shared characteristics and properties of the PR-39 derived oligopeptide family described in detail at page 25, lines 12-22 of the Specification text are overtly restated and individually set forth; and this antecedent description corresponds and

directly correlates with the requisite elements and specific limitations recited by presently amended claim 11 and newly added claim 16.

Equally important, the specified traits and attributes for the restricted membership of the PR-39 derived oligopeptide family also have been experimentally illustrated and empirically validated. Such direct evidence is overtly demonstrated by Experiment 6 and the use of PR-11, as described at page 46, lines 1-24 of the Specification. However, this particular working example and empirical demonstration of activity is not limited to merely this peptide alone. To the contrary, this exemplary embodiment merely evidences and empirically demonstrates the requisite structure, function, and pharmacological activity for the entire size-limited restricted family membership as defined by currently amended independent claim 11 and by the exemplary 8 amino acid residue length recited by new dependent claim 16.

Applicants and their undersigned attorney therefore respectfully submit and affirm that an objective review and dispassionate evaluation of the Specification text -which includes the range of written description, and the variety of illustrative details, and the body of empirical data collectively and cumulatively disclosed by the Specification text - reveal all the necessary knowledge and information concerning the structure, attributes and traits of the oligopeptides

defined by currently amended independent claim 11 and by new dependent claims 15 and 16 respectively, such that any ordinarily skilled practitioner could chose, prepare and use any of these embodiments at will.

For these reasons, applicants respectfully submit that all the presently pending claims meet and satisfy the enablement requirement for the invention in all respects. Accordingly, on the basis of all the foregoing, applicants request that the Examiners reconsider their position and withdraw this ground of rejection against the presently pending claims.

IV. The Rejection Under 35 U.S.C. 103(a)

The Examiners have rejected previously pending claims 11 and 12 respectively under 35 U.S.C. 103(a) as being unpatentable over the Ross *et al.* '233 patent [U.S. Patent No. 6,133,233]. The reasons and rationale given by the Examiners at pages 5-7 of the most recently received (final) Official Action are said to be factually derived from the Ross *et al.* '233 patent and include the following:

(i) Ross *et al.* teach the use of a 14 amino acid peptide for an *in-vivo* method of reducing reperfusion injury in a mammal which administers into the mammal's blood stream an effective amount of proline/arginine rich peptide; and

(ii) The 14 amino acid peptide disclosed by Ross *et al.* is a 95% query match with SEQ ID NO:3 recited by now cancelled claim 12.

However, applicants respectfully submit and maintain that the information provided by the Ross *et al.* '233 patent must be read as written in context; that the Ross *et al.* disclosure presents substantive limitations and specific constraints for the data and information actually disclosed; and the descriptive details in the Ross *et al.* '233 patent must be read and appreciated from the perspective of the person ordinarily skilled in this field.

Applicants therefore submit and affirm that a proper reading and objective review of the '233 patent reveals only the following.

1. The Ross *et al.* invention is described and defined solely as an in-vivo method of reducing reperfusion injury in a mammal resulting from temporary occlusion of a blood vessel and subsequent reperfusion thereof [Column 1, lines 17-20; Column 2, lines 22-26; claim 1]. The explicitly stated object and sole goal of the Ross *et al.* method is to inhibit the indices of reperfusion injury - *i.e.*, inhibiting the production of reactive oxygen species, inhibiting neutrophil adherence to endothelium, and inhibiting extravasation of neutrophils as a result of reperfusion [Column 1, lines 28-31and 42-63].

2. The Ross *et al.* method is directed solely and exclusively to reducing reperfusion injury in a mammal which results from the reperfusion of a temporarily occluded blood vessel. To achieve this purpose, the disclosed method clearly and overtly demands two things of the user: a means of access to the vascular blood system of the mammal having a temporarily occluded blood vessel; and a mode of administration for delivery of a suitable composition able to reduce reperfusion injury within the blood stream of the mammal's vascular system after the temporary occlusion in the blood vessel has been removed.

For this reason, the Ross *et al.* method as described and defined by the '233 patent explicitly sets forth two carefully recited manipulative steps: administering into the mammal's bloodstream a reperfusion injury-reducing amount of a peptide having up to about 50 amino acid residues, at least 65 % of which are proline and arginine residues; and allowing the peptide administered to the blood to come into effective contact with the temporarily occluded blood vessel in order to minimize the degree of reperfusion injury [Column 2, lines 22-32; Claim 1].

3. The Ross *et al.* method is dependent upon an ability to counteract the effects of oxygen-derived free radicals which are

released during reperfusion injury, after the temporary occlusion of a blood vessel has been removed. These oxygen-derived free radicals are said to be the primary mechanism of oxidative damage to cell structures; and are caused by reactive oxygen species (such as a superoxide ion) which are central to these events during reperfusion of temporarily occluded blood vessels [Column 1, lines 47—54 and 64-67]. For this reason also, the experiments and empirical results analytically measured the generation of reactive oxygen intermediate species [Column 5, lines 52-60].

4. A number of markedly different compositions of matter are deemed to be suitable for administration to the living mammal for reducing reperfusion injury resulting from temporary occlusion of a blood vessel by Ross *et al.* These include Bac 5, Bac 7, C7 and PAF [see Fig. 5].

Included among these also are the "synducins" – that is, PR-39 polypeptide and its longer-length analogues which were known previously to induce the expression of proteoglycans in mesenchymal cells. The structure of the "synducins", PR-39 polypeptide and its longer-length analogues, are expressly incorporated by reference into the Ross *et al.* Specification via PCT Publication WO 96/09322, which provides the following additional points of information:

(i) The PR-39 amino acid sequence must be employed at a minimum size as a 39 amino acid residue sequence in order for the desired biological activity to be demonstrated;

(ii) The entire 39 amino acid sequence of PR-39 can be part of a larger sized molecule, such as a fusion protein or when a mobilized to an inert substrate or targeted using a specific ligand, as part of a longer length protein;

(iii) The entire PR-39 peptide and any of its longer length analogues are collectively identified as "synducins" — all of which are characterized by a specific biological activity and a particular mechanism of action;

(iv) The "synducin" characteristic biological activity and specified mechanism of action are the inducement of syndecan-1 and syndecan-4 expression on the surface of mesenchymal cells. This is achieved via specific inducement of syndecan-1 and syndecan-4 mRNA within cells; or by an increase in the level of cell surface heparan sulfate and rapid uptake of such heparan sulfate into mesenchymal cells to a saturation level; and

(v) To be biochemically active, "synducins" must include a specific and lengthy amino acid sequence which is: Pro-Pro-X-X-Pro-Pro-X-X-Pro and Pro-Pro-X-X-X-Pro-Pro-X-X-Pro, where X is any amino acid.

5. The description and evidence disclosed by the Ross *et al.* '233 patent, however, increases the minimal structural requirements for the peptide compositions to be administered in-vivo for reducing reperfusion injury after temporary occlusion of a blood vessel. In particular, to be suitable for use in the Ross *et al.* method, the composition demonstrably must be:

(a) A peptide preferably comprising up to 50 amino acid residues, wherein at least 60 percent of such residues are proline and arginine residues. In preferred forms, the proline and arginine residues will constitute from 65-80 percent of the total residues in the composition [Column 2, lines 32-55]; and

(b) A peptide which has at least one amino acid sequence of -PXXP-, and preferably at least four such sequences of -PXXP-, wherein P is a proline residue and X is any amino acid residue. Moreover, these peptides should have one or more basic residues within six residues (and preferably within three residues) from both the starting and terminal proline residues of the —PXXP- sequence. Thus, each peptide composition suitable for administration should contain a sequence such as $X_1X_2X_3X_4X_5X_6PXXPX_7X_8X_9X_{10}X_{11}X_{12}$ where such or all of the $X_1$-$X_{12}$ amino acid residues are basic residues [Column 2, lines 56-76; Column 3, lines 1-11]. It is explicitly noted that the requirement for the —PXXP- structure is critical for activity if such a peptide

structure is to be effective in-vivo for reducing reperfusion injury [Column 3, lines 12-34].

6. The disclosure of the '233 patent also presents several experiments and empirical data which demonstrate the value of PR-39 and its structurally related peptides in the inhibition of the indices of reperfusion injury after temporary occlusion of a blood vessel. These experiments clinically evaluate the activity of PR-39 polypeptide and other peptides via: the generation and quantitative measurement of reactive oxygen release, as shown by Example 1; measurements of neutrophil adherence to postcapillary venules; preventing the loss of vascular integrity, as shown by Example 2; and inhibition of superoxide anion production and neutrophil chemotaxis, as shown by Example 3 [Columns 5–8 respectively].

Also, as expressly stated therein, pretreatment of living subjects prevented loss of vascular integrity resulting from reperfusion injury and blocking reperfusion-induced production of reactive oxygen, neutrophil adhesion and loss of vascular integrity [Column 6, lines 62-76]. Similarly, such peptides are found to be chemotactic for neutrophils when used alone, but are capable of acting as inhibitors when used in combination [Column 8, lines 63-76].

Lack of relevance for the Ross *et al.* '233 patent

This factual summary presents the total quantum and quality of information which is taught and/or suggested by the disclosure of the Ross *et al.* '233 patent to persons of ordinary skill in the technical field. The major thrust and underlying rationale of the rejection stated by the Examiners thus rest entirely on (a) the bare fact that a 14 amino acid residue peptide is disclosed as a composition of matter; and (b) an Examiner initiated mathematical analysis of the residue sequence for the 14 amino acid residue peptide reveals a 92 percent match with SEQ ID NO:3, the 15 amino acid residue exemplary embodiment recited by now cancelled claim 12. However, neither of these views and positions bear on or have relevance to applicants' claimed invention as now re-defined by currently amended claim 11or new claims 15 and 16.

In particular, applicants respectfully maintain that none of the information disclosed by the Ross *et al.* '233 patent pertains to the re-defined, restricted peptide size requirement, nor can serve as a basis for inferring any pharmacological activity, nor can suggest any specific functions and capabilities similar to those explicitly demanded by currently amended independent claim 11 and exemplified by new claims 15 and 16. Equally important, no mathematical analyses based on homology can provide a substantive basis for predicting the

presence or absence of pharmacological activity in a peptide structure, nor be a guide for establishing a structure/function formula which can accurately forecast the presence or absence of specific functions and capabilities for a particular oligopeptide.

The requisite attributes and characteristics of applicants' invention as currently claimed thus cannot be inferred or predicted by the Examiners with any degree of certainty. The underlying rationale stated and employed by the Examiners therefore constitutes mere guesses and speculation; and these are not proper or acceptable substitutes for reliable evidence or trustworthy facts.

The proper legal standard for non-obviousness

Applicants also wish to summarize briefly what are the legal standard for determining non-obviousness. As a matter of long established law, the proper legal basis and standard for determining obviousness under 35 U.S.C. 103(a) is as follows: Where applicant's claimed subject matter can be rejected as obvious in view of a single reference or a combination of prior art references, a proper analysis must consider inter alia two factors: (1) whether the prior art of record would have suggested to those of ordinary skill in the art that they should make and use the claimed article or claimed composition; and (2) whether the prior art would also have revealed that in so

making and using, those of ordinary skill would have a reasonable expectation of success [In re Dow Chemical Company, 5 USPQ 2d 1529 (Fed. Cir. 1988)].

Note that both the suggestion and the reasonable expectation of success must be found within the prior art reference itself and not in applicant's disclosure [In re Vaeck, 20 USPQ 2d 1438 (Fed. Cir. 1991)]. Equally important, the same inquiry must be carried out in the context of a purported "obvious modification" of the prior art information. The mere fact that the prior art might be modified in the manner suggested by the Examiner does not make that modification obvious unless the prior art itself suggested the desirability of the modification [In re Fritch, 23 USPQ 2d 1780 (Fed. Cir. 1992) and the references cited therein].

Applicants therefore respectively submit that the Examiners' stated views and conclusions in the most recently received (final) Official Action do not pertain and do not satisfy the objective legal standard required for a conclusion of obviousness.

In applicants' view, the the Ross *et al.* '233 patent is no longer either relevant or material to the re-defined invention recited broadly by presently amended independent claim 11; and does not come within

the purview, directly or indirectly, of newly added dependent claims 15 and 16. Accordingly, for these reasons, applicants respectfully submit and affirm that presently amended claim 11and newly added dependent claims 15 and 16 are therefore now allowable.

In view of the above discussion and detailed review, applicants believe that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiners are invited to call applicants' undersigned attorney should they feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted,

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